DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

T2101M

Food and Drug Administration
Center for Biologics Evaluation and Resea
1401 Rockville Pike
Rockville MD 20852-1448

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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Diana Goroff, Ph.D.
Vice President, Operations
IntraCel Corporation
1330 Piccard Drive
Rockville, MD 20850

Dear Dr. Goroff,

During the period from March 3 to April 22, 1998, Ms. Marya Ricks and Ms. Christine Whitby, investigators from the Baltimore District Office of the Food and Drug Administration (FDA), met with you to examine records relating to the use of ——————— ——————— under the Biologics Licensing Application, BLA ———

We acknowledge the receipt of a letter from IntraCel to the FDA, dated May 19, 1998, (Attachment A) which addresses the inspectional observations on the FDA Form 483 issued on April 22, 1998 (Attachment B).

Based upon review of the FDA Form 483 (Attachment B), the establishment inspection report of IntraCel Corporation, the letter from IntraCel to the FDA dated May 19, 1998 (Attachment A), and the inspection reports of three clinical sites (Site ———————; Site ———————: Site ———————), there are significant deviations from applicable federal regulations as published in Title 21, Code of Federal Regulations, Part 312 [21 CFR 312]. These deviations include, but are not limited to the following:

1. The sponsor, IntraCel, did not insure that the general investigational plan and protocols were followed. [21 CFR 312.50.]

   a. The sponsor modified the general investigational plan by terminating Site — because of the very low sensitivity of the ——————— ———————, scan results. FDA Form 483, Item (1.a): **"...FDA investigators were verbally informed that Site — was terminated based on the fact that mucin-producing adenocarcinomas were found in these patients."**

i. On April 29, 1994, a ——— (Site — memorandum reports ——— scan sensitivities of 4% and 6% for Planar and SPECT imaging, respectively. According to the memorandum which was submitted to the FDA by the sponsor in Attachment A, "It has become apparent that this ——— is not suitable for detecting mucinous peritoneal carcinomatosis." The sponsor did not inform the FDA of the reason for termination of this site until it was revealed during the inspection of the sponsor, four years after termination.

ii. Since the diagnosis of "mucinous peritoneal carcinomatosis" was not an exclusion criterion for Protocol — the sponsor modified the general investigational plan for Site ——— by terminating this site for enrollment of subjects with this diagnosis.

b. FDA Form 483, Item (1.b): **"Sponsor did not have consistent procedures or criteria for terminating sites."**

i. The sponsor agrees that there is no standard operating procedure for the termination of clinical sites. In Attachment A, the sponsor says that IntraCel is in the process of preparing a standard operating procedure for this purpose which will include "the procedure for terminating a study site, communication with the investigator, IRB and/or FDA, and notification of appropriate study personnel regarding the termination".

ii. After the termination of Site — there is no documentation that the sponsor amended Protocol — to exclude the enrollment of subjects with "mucinous peritoneal carcinomatosis". The sponsor selectively modified the general investigational plan in terminating Site —

c. The sponsor modified the general investigational plan by performing an interim statistical analysis, and then placing — sites on "hold" based on the results of this analysis.

i. The sponsor performed an interim statistical analysis on a group of subjects enrolled in Protocol — Results of the interim statistical analysis are given in the memorandum entitled "Interim Analysis of the — Phase III Study", dated October 31, 1994. (Attachment C) During the inspection of the sponsor, FDA investigators were told that the intent of the analysis was to determine the sensitivity and specificity of the product, and to see if the sample size needed to be adjusted. The sponsor did not notify the FDA about the results of this interim statistical analysis until the inspection of the sponsor in 1998.

ii. In the interim statistical analysis, — sites (Site 101— ——— Site 110— ——— ; and Site 117—. ——— ——— ——— were found to be "low in detecting abdominal lesions". The sponsor modified the general investigational plan when Dr. Robert L. De Jager, Director of Medical Research for the sponsor, placed these three sites on "hold", suspending the ongoing studies. (Attachments D, E, and F) This occurred on November 1, 1994, one day after the date of the "Interim Analysis" memorandum. The sponsor failed to notify the FDA that these sites had been placed on "hold".

iii. The sponsor failed to include all sites under Protocol — in the interim analysis. While the "Interim Analysis" memorandum documents that three sites had a low sensitivity for the detection of abdominal tumors with ——— it does not include the site with the lowest sensitivity (4-6%), ——— 'Site —'.

d. With regard to placing sites on "hold", FDA Form 483, Item (1.c) says: **"There is no written criteria for putting sites on 'hold', or documentation that the IRBs were notified of the 'hold' status. There were no written instructions informing investigators of what they should or should not do while on 'hold', nor were they notified in writing when they were removed from 'hold' status. However, patient treatments were resumed at the three sites after the sites re-evaluated their readings of scans during a meeting with the sponsor and changed them to agree with Sponsor-completed Data Clarification Forms which the investigator was to sign and date. This practice is inconsistent with Section 6.4 of the study protocol that the patient's 'true status' will be determined by surgery. Sites ——— were placed on 'hold' after an interim analysis conducted by the sponsor showed that results of scans at these three sites were 'significantly less sensitive' than those of the other sites. Eight false negatives and four false positives were reversed after review of scans during the sponsor's medical monitoring review."**

i. The sponsor modified the general investigational plan by placing three sites on "hold" without a standard operating procedure for this purpose. In Attachment A, the sponsor says that IntraCel is currently in the process of preparing a standard operating procedure for placing sites on "hold".

ii. After placing the three sites on "hold", the sponsor requested that clinical investigators change false negative and false positive ——— ') scan results in order to raise the sensitivity of the investigational product which had been calculated in the interim analysis. The sponsor modified the general investigational plan by asking clinical investigators to change ——— scan results on the Case Report Forms without a protocol for implementing these changes. The sponsor then submitted these changed results to the FDA in BLA ———

iii. There is no documentation that the "hold" status was ever rescinded at any of these three sites. Nor is there any record of the notification of the clinical investigators to resume the accrual and infusion of subjects. Nevertheless, enrollment resumed after clinical investigators made the changes requested by the sponsor on the Data Clarification Forms completed by the sponsor. The sponsor failed to report this change in the general investigational plan to the FDA.

e. The sponsor modified the general investigational plan at Site — to allow a subinvestigator to change the ——— scan results of the Principal Investigator while that site was on "hold".

i. Representatives of the sponsor scheduled a medical site visit in (Site —) on November 2, 1994, as indicated in the "hold" letter (Attachment D). Data Clarification Forms dated November 2, 1994, were filled out for both subject ' —— ' and subject ' —— changing the results for three lesions from False Negative to True Positive. Dr. (Principal Investigator, Site —— told the FDA that the Data Clarification Forms were signed by Dr. ——— ', a research associate, and not by himself. In addition, Dr. ——— said that his original interpretation should stand.

ii. In Attachment A, the sponsor said that, with regard to the interim analysis, all data entered for analysis was approved by the Principal Investigator. The sponsor failed to notify the FDA that these changes at Site —— were not made by the Principal Investigator, and that the Principal Investigator did not agree with the changes for either subject.

iii. The sponsor failed to insure that the BLA ——— Line Listings were consistent with the Principal Investigator's evaluation of the ———) scans. The Final Report for Site —, completed by the Principal Investigator, Dr. ——— includes his original results for the ——— scans both for subject ——— and for subject ——— This Final Report was submitted to the sponsor and the Institutional Review Board. The ——— ——— scan results in the Final Report differ from the results in both the Data Clarification Forms and the BLA ——— Line Listings.

f. FDA Form 483, Item (3.): **"Changes to the investigational plan were not reported to the FDA or IRBs in that an additional Medical Review of completed Case Report Forms was conducted by the sponsor which was not initially part of the study, but was introduced in September 1994 as an administrative procedure. As a result of these reviews Data Clarification Forms were generated which were sent to Investigators suggesting possible changes."**

i. The position of Dr. ——— the Medical Reviewer, was not a part of the protocol. The sponsor modified the general investigational plan in order to have Dr. ——— perform the Medical Review of the completed Case Report Forms.

ii. During the inspection of the sponsor, the FDA investigators were told that the medical review was put in place in September 1994 because there was no one to perform medical reviews at the firm after the departure of the medical directors. However, the sponsor also said that Dr. Robert De Jager was the Medical Director from January 5, 1984, through March 31, 1995, a period which includes the date of the Medical Review. During that time, Dr. De Jager placed three sites on "hold" as a result of the interim statistical analysis.

g. FDA Form 483, Item (1.b): **"In addition, at Site ——— ———, the principal investigator did not follow the protocol in that antibody scan reports were not completed concurrently with patient antibody scan readings despite repeated requests from the sponsor. This site was not terminated nor were the nuclear reports completed until after the study was finished."**

i. One of the objectives of Protocol —— was the determination of the "sensitivity, specificity, and accuracy of ———— . As part of the statistical plan for Protocol ———— ———— scans are to be compared to CT scan results alone, as well as to the combination of CT scan plus ———— ————) scan results. In order to determine the sensitivity of the investigational product and compare the results with CT scan findings, ———— scans had to be read independently of other imaging modalitites, as well as surgical/histopathologic results. Dr. —— (Sub-investigator, Site —) told the FDA that he did not prepare ———— ———— scan reports after his initial evaluation of the ———— images. Instead, he usually observed the surgery for each subject, consulted with the surgeon, and then documented the ———— ———— scan results in the Case Report Forms two to three weeks after the imaging was completed. Subsequently, Dr. —— reread the ———— ———— , making corrections on the Case Report Forms. Dr. —— told the FDA that the———— ————)) scan reports usually did not correlate with the scan results in the Case Report Forms. The sponsor modified the general investigational plan by allowing Dr.—— to interpret the ———— scans after surgery.

ii. The sponsor made a further modification of the general investigational plan by allowing clinical investigators to prepare ———— ———— scan reports months after the studies were completed. Dr. — ; told the FDA that the time from the "Date of imaging" until the "Date of report" varied from nine days up to twelve months for ———— scan results at his site.

h. FDA Form 483, Item (1.b): **"...Site — was terminated when scheduled surgeries were cancelled after infusion, while Site———— ———— was allowed to reinfuse patients and proceed with the study after surgeries were cancelled."**

i. The sponsor modified the general investigational plan to allow two sites (—, and — , to enroll subjects twice under Protocol ———— give them a second infusion of ———— ———— , without notifying the FDA prior to instituting this change.

ii. Subjects ——— upon second enrollment), ——— and ——— were enrolled on two different dates under Protocol — and each received two separate infusions of ——— ——— The sponsor failed to notify the FDA that the same subjects appear more than once in the BLA Line Listings.

2. The sponsor (IntraCel) failed to perform adequate review of on-going investigations [21 CFR 312.56.]

a. FDA Form 483, Item (4.): **"There was no Curriculum Vitae, nor an FDA 1572 completed for all investigators and sub-investigators that participated in the study at Site —."** FDA Form 1572 from Site — ——— did not include the names of the physicians, Dr. ——— and Dr. ——— who assisted the Principal Investigator, Dr. —— and the Sub-investigator, Dr. —— in this study, even though all four doctors were listed on the "Authorized Representative Signature Page", and all four participated in the study.

b. The sponsor failed to insure that a clinical investigator was aware of his responsibilities for participation in an IND study. During the FDA inspection of Site———, for Protocol ——, over the period June 9-13, 1997, Dr. ———, the clilnical investigator stated that he did not understand his responsibilities under the Food, Drug, and Cosmetics Act. In addition, the following were noted:

i. Dr. ——— had a limited understanding of English, and had difficulty communicating with the FDA inspector. (No translator was available.) However, the only copies of the Protocol and Amendments available at his site were in English.

ii. Dr. ——— stated that he was not aware of Amendment #1, dated September 1, 1994, and suggested that it might have been filed in his records by the sponsor's monitor. This Amendment had a fax date of June 5, 1997, four days prior to the initiation of the inspection and the date of the most recent audit by the sponsor's representative.

iii. The sponsor failed to insure that the ——— ——— ——— scan reports prepared by Dr. ——— were accurate with respect to the time between the injection of the investigational product and imaging of the subject. Protocol — stated that imaging was to be performed ——— after administration of ——— The reports, on the other hand give the time of imaging as ——— or subjects ———

c. The sponsor does not have a Standard Operating Procedure for tracking serious adverse events. FDA investigators were told this by the sponsor during the inspection of IntraCel.

d. The sponsor did not tell the FDA that lesions seen on the ——— ——— scans for subject —— may have represented bronchogenic carcinoma, as well as adenocarcinoma of the colon.

i. According to the sponsor, subject —— had a serious adverse event (death), not related to the to the infusion of ———. On October 3, 1995, Dr. ——, the Medical Reviewer for the sponsor, determined that the "patient's death was due to advanced and terminal adenocarcinoma of the colon with metastases and has nothing to do with the infusion of ———." However, the Certificate of Death for subject ——, dated May 9, 1995, lists the following causes of death: "Cardiopulmonary arrest. Bronchogenic carcinoma metastatic to lungs and brain."

ii. The BLA —— Line Listings for subject —— show three lesions, S1— ——, S2— ——— and S3— ——. The histopathologic results for S2 and S3 were "No Tissue Available" and "Not Done", respectively. Since there are no pathology reports for either S2 or S3, and since this subject had metastatic bronchogenic carcinoma as well as colon cancer, S2 and S3 may represent colon cancer, bronchogenic cancer, or benign lesions.

e. In the BLA——— Line Listings for both Protocol —— and Protocol —— multiple lesions are coded as "No Tissue Available" or "Not Done" under "Pathology". In the absence of pathologic confirmation, the etiology of these lesions cannot be determined, especially in those subjects with multiple malignancies.

3. The sponsor did not require clinical investigators to provide final reports upon completion of the studies. [21 CFR 312.64.c]

a. FDA Form 483, Item (5.): "There were no final reports for ——— sites that participated in the studies."

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Federal Food, Drug, and Cosmetics Act, as well as the Public Health Service Act, and relevant regulations. Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step taken to prevent a recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved.

Failure to achieve prompt correction may result in enforcement action without further notice. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, termination of Investigational New Drug Applications (IND's) and/or injunction. Your written response should be sent to me at the following address:

Office of Compliance, HFM-600
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 400S
Rockville, Maryland, 20852-1448

Sincerely,

Elaine Knowles Cole
Acting Director
Office of Compliance and Biological Quality
Center for Biologics Evaluation and Research

Attachments:
Attachment A: Letter from IntraCel to the FDA, dated May 19, 1998.
Attachment B: FDA Form 483, Inspectional Observations, dated April 22, 1998.
Attachment C: AKZO memorandum, "Interim Analysis of the 9208 Phase III Study - Sensitivity of OncoSPECT to Detect Lesions in Abdomen", dated October 31,1994.
Attachment D: AKZO letter from Robert L. De Jager, M.D., F.A.C.P., to ———— , M.D., dated November 1, 1994.
Attachment E: AKZO letter from Robert L. De Jager, M.D., F.A.C.P., to ———— M.D., dated November 1, 1994.
Attachment F: AKZO letter from Robert L. De Jager, M.D., F.A.C.P., to ——— M.D., dated November 1, 1994.

Enclosures:
Enclosure 1: 21 CFR Part 312 (revised as of April 1, 1996)